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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
SULLIVAN, DANIEL M

ART UNIT	PAPER NUMBER
1636	10

DATE MAILED: 12/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/729,644	Applicant(s) PIERCE ET AL.	
	Examiner Daniel M Sullivan	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-71 and 98-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-71 and 98-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 November 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☒ Notice of References Cited (PTO-892)
2)☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5,6* .
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

This is a First Office Action on the Merits of the application filed November 30, 2000, which claims priority U.S. Provisional Patent application 60/168,470 filed December 1, 1999. This Office Action is responsive to the Response to Restriction Requirement filed October 7, 2002 (Paper No. 9). Claims 72-97 were canceled in Paper No. 9. Claims 1-71 and 98-104 are pending and under consideration in the application.

Election/Restrictions

Applicant's election of Group I (Claims 1-71 and 98-104) in Paper No. 9 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Drawings

The drawings filed on November 30, 2000 are acceptable subject to correction of the informalities indicated on the attached "Notice of Draftperson's Patent Drawing Review," PTO-948. In order to avoid abandonment of this application, correction is required in reply to the Office action. The correction will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front

of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. **Corrections other than Informalities Noted by Draftsperson on form PTO-948.**

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-71 and 98-104 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention: The claims are directed to an *in situ* bioreactor adapted for systemic delivery of bioactive agents and a device comprising a biocompatible substance capable of cellular infiltration, a first nucleic acid molecule encoding a cell growth stimulating agent and a second nucleic acid molecule encoding a bioactive agent.

Breadth of the claims: It is clear from the disclosure, which provides instructions on delivery of the claimed device into patients and descriptions of several pathological conditions that might be treated using the claimed device, that the claims are directed to a device for the therapeutic delivery of nucleic acids. The specification suggests no use for the device other than

therapy; therefore, the claimed invention encompasses a device having a single utility, said utility being gene therapy. The enabling disclosure must, therefore, teach the skilled artisan how to use the claimed invention for the purpose of gene therapy.

State of the prior art: *State of the prior art and level of predictability in the art*: At the time of filing, *in vivo* gene therapy utilizing the direct administration of recombinant nucleic acids, regardless of the mode of delivery (e.g. adenovirus, retrovirus, liposome), was considered to be highly unpredictable. Verma et al. states that, "[t]he Achilles heel of gene therapy is gene delivery...", and that, "most of the approaches suffer from poor efficiency of delivery and transient expression of the gene" (Verma et al. (1997) *Nature* Volume 389, page 239, column 3, paragraph 2). Marshall concurs, stating that, "difficulties in getting genes transferred efficiently to target cells- and getting them expressed- remain a nagging problem for the entire field", and that, "many problems must be solved before gene therapy will be useful for more than the rare application" (Marshall (1995) *Science*, Vol. 269, page 1054, column 3, paragraph 2, and page 1055, column 1).

Orkin *et al.* further states in a report to the NIH that, " ... none of the available vector systems is entirely satisfactory, and many of the perceived advantages of vector systems have not been experimentally validated", and that," [w]hile the expectations and the promise of gene therapy are great, clinical efficacy has not been definitively demonstrated at this time in any gene therapy protocol" (Orkin *et al.* (1995) Report and recommendations of the panel to assess the NIH investment in research on gene therapy, page 1, paragraph 3, and page 8, paragraph 2).

Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck *et al.* (1996) Goodman & Gilman's The

Pharmacological Basis of Therapeutics, 9th Edition, Chapter 5, McGraw-Hill, NY, explains, "the delivery of exogenous DNA and its processing by target cells require the introduction of new pharmakokinetic paradigms beyond those that describe the conventional medicines in use today". Eck *et al.* teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (see Eck *et al.* bridging pages 81-82).

Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al. teaches that weak promoters produce only low levels of protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein expression be achieved (Verma et al., *supra*, page 240, column 2). Verma et al. further warns that, "...the search for such combinations is a case of trial and error for a given type of cell" (Verma et al., *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al. Human gene Therapy, vol. 7, pages 1781-1790, September 1996, see page 1789, column 1, first paragraph).

Beyond the technical barriers common to all gene therapy approaches, each disease to be treated using gene therapy presents a unique set of challenges that must be addressed individually. The specification asserts that the claimed device can be used in the treatment of a wide range of pathologies. However, Rubanyi (2001) *Mol. Aspects Med.* 22:113-142 teaches, "each disease indication has its specific technical hurdles to overcome before gene therapy can become successful in the clinic" (page 131, third full paragraph). Rubanyi states, "the most promising areas for gene therapy today are hemophilias, for monogenic diseases, and cardiovascular disease (more specifically, therapeutic angiogenesis for myocardial ischemia and peripheral vascular disease...) among multigenic diseases" (page 113, fourth paragraph). As of the filing date of the instant application, however, even these most promising areas presented barriers to successful gene therapy that could not be traversed by routine experimentation.

With regard to hemophilia, Schwaab *et al.* (2001) *Semin. Thromb. Hemost.* 27:417-424 teach that immune response against gene therapeutically administered Factor VIII and Factor IX compromised the success of therapy in many animal studies and that, "the situation is still more complicated by the fact that hemophilia B-affected dogs that have been intravenously treated with canine Factor IX protein without immune response against canine Factor IX develop antibodies when treated by gene therapy" (page 421, first paragraph in column II). Schwaab *et al.* also affirms that gene delivery remains a substantial problem in the development of gene therapy for hemophilia (see especially the second paragraph in column 2 on page 421). In subsequent discussion of ongoing clinical trials of gene therapy for hemophilia A and B, Schwaab *et al.* teach that, as of 2001, the effectiveness of gene therapy as a treatment for hemophilia had not been established (see beginning the final paragraph on page 421 and

continued through the first paragraph of the second column on page 422). These teachings demonstrate that, as of the time of filing, successful treatment of hemophilia using gene therapy was unpredictable regardless of the delivery method employed.

With regard to gene therapy of ischemia, Rissanen *et al.* (2001) *Eur. J. Clin. Invest.* 31:651-666, teaches that although applications of therapeutic angiogenesis for ischemic disorders has established the proof of principle that exogenous growth factors can augment circulatory defects in animals and man, many important questions remain to be addressed. "Firstly, mechanisms of collateral growth by exogenous growth factors are still unclear...[a]dditional factors...may be required for collateral formation and maintenance of functional blood vessels. Secondly, the persistence of new vessels is unknown after transient gene expression. Thirdly, improvement is needed in gene transfer efficiency..." (paragraph bridging pages 659 and 660). Emanueli *et al.* (2001) 133 :951-958 further teach that, "[d]elivery of angiogenic inducers...in ischaemic tissues allows rescue of blood perfusion. However, angiographic studies clearly show that the newly formed vasculature is abnormal and not well organized as in normal tissues...resembling the characteristics of leaky haemangiomas..." (page 955, the paragraph bridging columns 1 and 2). These teachings show that, even in an area of gene therapy considered promising, significant obstacles to successful therapy remained well after the effective filing date of the instant application.

Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art at the time of filing was extremely low.

Amount of direction provided by the inventor and existence of working examples: The instant disclosure provides a description of various biocompatible substances capable of cellular infiltration, examples of growth stimulating agents and bioactive agents, and prophetic statements indicating that these agents can be combined to treat a wide range of pathologies. Applicants then describe a series of experiments wherein adenovirus vectors comprising PDGF-BB, luciferase, Factor VIII and EPO transgenes or nonviral vectors comprising Factor VIII or EPO are injected into implanted PVA sponges. The data presented in the application, shown in figures 2A, 2B, 3A and 3B, demonstrate that injection of the vector comprising the PDGF transgene results in increased granulation tissue around the sponge, and that coadministration of the vector comprising the luciferase transgene with the PDGF transgene results in increased luciferase expression relative to administration of the vector comprising the luciferase transgene alone. No results are described for the vectors comprising the therapeutic proteins and no data are presented that would indicate that the claimed apparatus provides any advantage over the known delivery methods (e.g. provides more extended transgene expression or provides transgene expression at therapeutic levels) which would enable the skilled artisan to use the apparatus to treat conditions that heretofore were refractory to treatment by gene therapy.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the level of skill in the art is high, given the high degree of unpredictability in the gene therapy art, the skilled artisan would not be able to use the claimed device without first engaging in undue experimentation to devise a method of treatment. While it is relatively routine in the gene transfer art to achieve expression at non-therapeutic levels (i.e. levels providing no patentably useful phenotypic effect), the skilled artisan would have to engage

in trial and error experimentation to achieve expression of a particular molecule at levels sufficient for therapeutic effect. And, given the many factors affecting gene transfer and expression, *in vivo*, and the absence of existing working examples, the level of experimentation required is clearly beyond what is considered routine. Therefore, the teachings of the specification and prior art would not enable the ordinary skilled artisan to use the invention without undue experimentation.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

In the instant case, the claim is directed to a bioreactor comprising a mutated FGF-2 having the properties of a "growth stimulating agent" as the term is defined in the first full paragraph on page 8 of the specification. The claim thus encompasses a genus of bioreactors comprising any and all mutated FGF-2 molecules having the ability to promote cellular ingrowth/migration, survival/cellular maintenance, and/or proliferation either directly or

indirectly. The Written Description Guidelines state "when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus", "In an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436). The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics (see MPEP 2163 (ii)). In the first paragraph on page 28, applicant provides two examples of a mutant FGF-2 that has the activity of a growth stimulating agent (i.e. C78S and C96S) and cites prior art wherein these species were reduced to practice. Given that the claims encompass bioreactors comprising mutations at each and every amino acid in the FGF-2 sequence these two species are far from representative of the entire genus.

With regard to identifying characteristics, the Final Written Description Guidelines state that identifying characteristics include, "structure or other physical and/or chemical properties,...functional characteristics coupled with a known or disclosed correlation between function and structure or... a combination of such identifying characteristics..." (Federal Register, Vol. 66, No. 4, page 1106, column 3, second full paragraph). In order to fully describe the structure of a polypeptide, Applicant must describe more than simply the primary amino acid sequence, as the functionality of a polypeptide is comprised within its higher order structure (i.e. secondary and tertiary structure). Because it is presently impossible to envision the higher order structure of a polypeptide based on a description of its primary structure alone, the skilled artisan would not recognize that Applicant was in possession of the genus of any and all mutant FGF-2

polypeptides having the function of a growth stimulating agent based on a description of the primary structure of any and all mutant FGF-2 polypeptides. As indicated in the Guidelines cited herein above, a genus of polypeptides might also be adequately described by disclosure of structural characteristics coupled with correlation of those structural characteristics with functional properties of the polypeptide. In the instant case, the disclosure provides that FGF-2 polypeptides wherein either one of two identified cysteine residues are substituted with serine residues retain the function of a growth stimulating agent. There is nothing in the disclosure, however, that would allow the skilled artisan to extend this knowledge beyond the disclosed species.

An adequate written description of a polypeptide requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the polypeptide itself. It is not sufficient to define polypeptide solely by its principal biological property, i.e. it is a growth stimulating agent, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any polypeptide with that biological property. Also, naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. Thus, claiming all polypeptide's that achieve a result without defining what means will do is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)).

In view of these considerations, a skilled artisan would not have viewed the teachings of the specification as sufficient to show that the applicant was in possession of the claimed

invention commensurate to its scope because it does not provide adequate written description for the broad class of bioreactors comprising any and all mutated FGF-2 molecules having the ability to promote cellular ingrowth/migration, survival/cellular maintenance, and/or proliferation either directly or indirectly. Therefore, only the described bioreactor comprising the C78S and C96S mutant FGF-2 meet the written description provision of 35 U.S.C. §112, first paragraph.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5, 6, 8-10, 12, 13, 36 and 102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 5 and 6, as it depends from 5, are indefinite in their recitation of "PDGF family members". There is no antecedent for PDGF family members in claim 4, from which the claims depend. Amending claim 4 such that it is directed to "PDGF family members" would obviate this rejection.

Claims 8 and 9 and 10, as they depend from 8, are indefinite in their recitation of "FGF family members". There is no antecedent for FGF family members in claim 4, from which the claims depend. Amending claim 4 such that it is directed to "FGF family members" would obviate this rejection.

Claims 12 and 13, as it depends from 12, are indefinite in their recitation of "TGF family members". There is no antecedent for FGF family members in claim 4, from which the claims depend. Amending claim 4 such that it is directed to "TGF family members" would obviate this rejection.

Claim 36 is indefinite in its recitation of "anticoagulant" in line 1. There is no antecedent for "anticoagulant" in claim 35, from which claim 36 depends. It would appear that applicant intends that claim 36 be directed to a "coagulant" and amending the claim accordingly would obviate this rejection.

Claim 102 is indefinite in its recitation of an optional limitation. It is unclear how the claim further limits the base claim, claim 98, which is directed to a device comprising a first and second nucleic acid. Because open language is used in describing the device, claim 98 is already directed to a device that *optionally* comprises additional nucleic acid molecules. If Applicant's intention is to claim a device according to claim 98 and further comprising additional nucleic acid molecules, claim 102 should be amended such that the limitation is stated in definite terms (such as "...the device is supplemented with additional nucleic acids.").

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Note: The following rejection applies to the extent that the prior art discloses the same compositions and/or method embraced by the instant invention. The prior art rejection is not to be construed as an indication that the claimed or anticipated methods are *enabled* for the wide breadth of subject matter potentially embraced by the claims. The compositions and/or methods disclosed in the prior art are essentially enabled to the same extent as the instant specification, since there is no significant difference in the level of guidance presented in either case.

Claims 1-6, 8, 9, 11-13, 23-26, 39-43, 49-55, 57-67, 69 and 98-104 are rejected under 35 U.S.C. 102(b) as being anticipated by The Regents of the University of Michigan (WO 95/22611; hereinafter '611).

The claims are directed to an *in situ* bioreactor or "Bi-gene" device comprising a first nucleic acid molecule encoding a cell growth stimulating agent, a second nucleic acid molecule encoding a bioactive agent, and a biocompatible substance capable of cellular infiltration. The patent application '611 discloses a variety of growth stimulating agents, bioactive agents and biocompatible substances capable of cellular infiltration, and teaches combining the biocompatible substances capable of cellular infiltration with nucleic acids encoding the growth stimulating agents and/or bioactive agents and the implantation of the coated biocompatible substances capable of cellular infiltration into an animal (see throughout, especially the second full paragraph on page 7). In the paragraph bridging pages 18 and 19, '611 further teaches that the nucleic acids encoding growth stimulating agents and/or bioactive agents can be combined in a single application; thus, '611 teaches the "Bi-gene" device and *in situ* bioreactor of the instant application.

Specific embodiments of the bioreactor comprising various growth stimulating agents claimed in claims 2-14 are also disclosed in '611. See especially TGF (including TGF-β_1, TGF-β_2 and TGF-β_3), EGF, FGF (including FGF-2 and FGF-6), and PDGF disclosed in the paragraph bridging pages 13 and 14; BMPs disclosed beginning at the second full paragraph on page 14 and continued through the first paragraph on page 15; and antisense molecules disclosed in the paragraph bridging pages 7 and 8. The patent application '611 also teaches the use of cell retention agents such as collagen and adhesive polypeptides, and genes encoding cell retention agents such as chemotactic agents (see especially the second full paragraph on page 13). Also in the second full paragraph on page 13, '611 teaches the hormone PTH.

The patent application '611 also teaches the various vector constructs claimed in the instant application including nucleic acids linked to promoters (see especially page 21), virus vectors including adenovirus and retrovirus (see especially the first paragraph on page 8 and the first full paragraph on page 24). Many specific embodiments of the biocompatible substance capable of cellular infiltration are also disclosed in '611, including biological matrices, polymers, collagen (including type I and type II collagen), extracellular matrix, synthetic matrices, lactic acid polymers, block copolymers and acrylic ester polymers (see especially beginning on page 23 and continued through page 27) as well as biocompatible substances associated with an implantable device (see especially the first full paragraph on page 25).

Finally, beginning at the final paragraph on page 31 and continued through the final paragraph on page 33, '611 teaches kits based on the disclosed devices.

The devices and kits taught in the patent application '611 are the same as those taught in the instant application, therefore the limitations of the claims are met by '611.

Claims 1-9, 11-15, 23-26, 39-43, 49-55, 57-67, 69, 70 and 98-104 are rejected under 35 U.S.C. 102(e) as being anticipated by Goldstein *et al.* (1996) U.S. Patent No. 5,962,427 (hereinafter Goldstein *et al.*).

As described herein above, the claims are directed to an *in situ* bioreactor or "Bi-gene" device comprising a first nucleic acid molecule encoding a cell growth stimulating agent, a second nucleic acid molecule encoding a bioactive agent, and a biocompatible substance capable of cellular infiltration. Goldstein *et al.* discloses a variety of growth stimulating agents, bioactive agents and biocompatible substances capable of cellular infiltration, and teaches combining the biocompatible substances capable of cellular infiltration with nucleic acids encoding the growth stimulating agents and/or bioactive agents and the implantation of the coated biocompatible substances capable of cellular infiltration into an animal (see throughout, especially the fourth full paragraph in column 4). In the second full paragraph of column 17, Goldstein *et al.* further teaches that the nucleic acids encoding growth stimulating agents and/or bioactive agents can be combined in a single application; thus, '611 teaches the "Bi-gene" device and *in situ* bioreactor of the instant application.

Specific embodiments of the bioreactor comprising various growth stimulating agents claimed in claims 2-14 are also disclosed in Goldstein *et al.* See especially TGF (including TGF-β_1, TGF-β_2 and TGF-β_3), EGF, FGF (including FGF-2 and FGF-6), HGF and PDGF (disclosed beginning at the second full paragraph in column 14 and continued through the first paragraph in column 15); BMPs (disclosed in the fourth paragraph of column 21); and antisense and ribozyme molecules (disclosed in the fourth full paragraph in column 4). Goldstein *et al.* also teaches the

use of cell retention agents such as collagen and adhesive polypeptides, and genes encoding ell retention agents such as chemotactic agents (see especially the fourth paragraph in column 10). Also in the second full paragraph in column 14, Goldstein *et al.* teaches the hormone PTH.

Goldstein *et al.* also teaches the various vector constructs claimed in the instant application including nucleic acids linked to promoters (see especially the paragraph bridging columns 15 and 16), virus vectors including adenovirus and retrovirus (see especially the third full paragraph in column 15). Many specific embodiments of the biocompatible substance capable of cellular infiltration are also disclosed by Goldstein *et al.*, including biological matrices, polymers, collagen (including type I and type II collagen), extracellular matrix, synthetic matrices, lactic acid polymers, block copolymers and acrylic ester polymers (see especially beginning the second paragraph in column 11 and continued through the first paragraph in column 14) as well as biocompatible substances associated with an implantable device and medical devices such as sutures and wound dressings (see especially column 12 and the paragraph bridging columns 17 and 18).

Finally, in the first paragraph in column 11, Goldstein *et al.* teaches kits based on the disclosed devices.

The devices and kits taught by Goldstein *et al.* are the same as those taught in the instant application, therefore the limitations of the claims are met by Goldstein *et al.*

Conclusion

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
November 27, 2002

Anne-Marie Falk
ANNE-MARIE BAKER
PATENT EXAMINER